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Frequency and Distribution of Thin-Cap Fibroatheroma and Ruptured Plaques in Human Coronary Arteries

A Pathologic Study

Pavan K. Cheruvu, MSc,* Aloke V. Finn, MD,† Craig Gardner, PhD,‡ Jay Caplan, BS,‡ James Goldstein, MD,§ Gregg W. Stone, MD,‖ Renu Virmani, MD,¶ James E. Muller, MD‡

Boston and Burlington, Massachusetts; Royal Oak, Michigan; New York, New York; and Gaithersburg, Maryland

Objectives Our purpose was to quantify the frequency and distribution of suspected vulnerable lesions, defined as thin-capped fibroatheroma (TCFA) and ruptured plaque, in human coronary artery autopsy specimens.

Background Most acute coronary events and sudden death are believed to arise from rupture of a TCFA followed by thrombosis. Although there is general agreement that clinical events are usually caused by focal lesions, there is considerable debate over the relative importance of focal versus systemic factors in the pathogenesis of atherosclerosis.

Methods We longitudinally sectioned coronary arteries from 50 whole hearts taken from patients (mean age 73 years, 64% men) dying of cardiovascular (n = 33), noncardiovascular (n = 13), and unknown (n = 4) causes. A total of 3,639 longitudinal segments of length 3 mm were sectioned from 148 arteries, accounting for 10.9 m of total tissue length. Specimens were classified on the basis of histology and computer-aided morphometry.

Results Twenty-three TCFA and 19 ruptured plaques were found (mean ± SD: 0.46 ± 0.95 and 0.38 ± 0.70 per heart, respectively), and these lesions accounted for only 1.6% and 1.2%, respectively, of the total length of the coronary tree examined in patients dying of cardiovascular causes. The majority of TCFA and ruptured plaque localized in the proximal third of the major coronary arteries, and in 92% of cases these lesions clustered within 2 or fewer nonoverlapping 20-mm segments.

Conclusions The suspected precursors of rupture-mediated thrombosis occur in a limited, focal distribution in the coronary arteries. (J Am Coll Cardiol 2007;50:940–9) © 2007 by the American College of Cardiology Foundation

Rupture of an atheromatous plaque with superimposed thrombosis is the accepted cause of most acute coronary syndromes (ACS) and sudden coronary death (1–4). However, considerable debate exists regarding the number (5–8) and extent (9–11) of coronary plaques at risk of becoming culprit lesions.

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Atherosclerosis is now appreciated as a progressive, chronic, inflammatory disease (12,13) with systemic manifestations (14). Early markers of inflammation, such as fatty deposits (15), elevated C-reactive protein (16), and lymphocyte activation (17), can be observed throughout the coronary and peripheral systems of a single patient. It is not known, however, whether the areas at risk for rupture and thrombosis are as diffuse as the pattern of inflammatory involvement. A paradigm of diffuse coronary risk (18,19) is supported by observations of multiple complex plaques (20) and multiple ulcerations (5,21) in patients with ST-segment elevation myocardial infarction.

From *Harvard Medical School, Boston, Massachusetts; †Massachusetts General Hospital, Boston, Massachusetts; ‡InfraReDx, Inc., Burlington, Massachusetts; §William Beaumont Hospital, Royal Oak, Michigan; ‖Columbia University Medical Center and the Cardiovascular Research Foundation, New York, New York; and ¶CV Path, Gaithersburg, Maryland. This work was supported by funding from InfraReDx, Inc. Mr. Cheruvu is a former employee of InfraReDx Inc.; Dr. Gardner is an employee of InfraReDx Inc.; Mr. Caplan is an employee of InfraReDx Inc. and owns stock in InfraReDx Inc.; Dr. Goldstein is a consultant for and owns stock in InfraReDx Inc.; Dr. Stone is a consultant for Volcano, Abbott Vascular Devices, Boston Scientific Corp., Thermocore Ltd., and Bristol-Myers Squibb Imaging, and owns stock in Thermocore Ltd. and Prescient Medical; Dr. Virmani is on the medical advisory board of InfraReDx Inc.; and Dr. Muller is the CEO and founder of InfraReDx Inc.

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Alternative hypotheses that allow for a focal distribution of risk include: 1) multifocal injury, wherein many small arterial segments throughout the coronary tree are predisposed to inflammation, disruption, and thrombosis; and 2) limited focal injury, a condition of diffuse inflammation that is aggravated at 1 or a few "hot spots" toward disruption and thrombosis. Supporting the latter view, clinical experience shows that culprit lesions responsible for ACS and sudden death usually occur singly (20), and these lesions cluster proximally in a few millimeters of the responsible coronary vessel (22,23). Limited data from autopsy studies, which link thin-cap fibroatheromas (TCFAs) to plaque rupture and intracoronary thrombosis (24), suggest that TCFA are sparsely (3,8) and proximally (25) distributed in victims of sudden coronary death.

Whether the precursors to intracoronary thrombosis are focally or diffusely distributed in the coronary tree has major implications for ongoing efforts to identify (26–30) and stabilize (31–34) vulnerable plaques before they cause coronary events. We used a novel longitudinal sectioning with computer-aided morphometry to maximize detection of TCFA and ruptured plaque in this 3-vessel examination of autopsied human hearts.

Abbreviations and Acronyms

ACS = acute coronary syndrome
CV = cardiovascular
MCFA = medium-capped fibroatheroma
TCFA = thin-capped fibroatheroma
ThCFA = thick-capped fibroatheroma

Methods

Study population. Between October 2002 and February 2004, 50 whole human hearts including proximal aorta were received from National Disease Research Interchange, in accordance with applicable informed consent and privacy regulations. National Disease Research Interchange is a nonprofit tissue procurement agency sponsored by the National Institutes of Health. We requested whole hearts involving a mix of cardiovascular (CV) and non-CV causes of death. No exclusions were requested for cause of death, past medical history, or gender. Hearts were immersed in 4°C saline during storage and transport, and studied within 96 h of death. Upon receipt, epicardial coronary arteries were excised and processed for histology, as described in the following text. None of the donor cardiac tissues were saved, but histologic slides of coronary arteries and fixed segments of arteries were retained and banked.

Age, gender, medical history, and cause of death were obtained from the National Disease Research Interchange. The following terms were designated as CV cause of death based on data submitted by the National Disease Research Interchange: "myocardial infarction," "cerebrovascular accident," "cardiac arrest," "cardiomyopathy," "congestive heart failure," and "other cardiac."

Tissue excision and processing. Upon receipt, each whole heart was dissected to remove the right coronary artery, left circumflex artery, and left anterior descending artery. Dissection of the right coronary artery began at the coronary ostium in the proximal aorta, and dissection of the left anterior descending and left circumflex arteries began at the ostium with the left main artery. In all locations, dissection ended where the lumen diameter was insufficiently large to permit excision with simple surgical tools (<0.5 mm). Arterial samples were cut into 20-mm longitudinal segments and washed with saline to remove residual intraluminal thrombus or postmortem clots. Approximately 2.5 mm on each end of the 20-mm segment was immobilized and, therefore, not included in the analysis. Each segment was opened lengthwise by a longitudinal cut to expose the vessel lumen (Fig. 1). Gross specimens were photographed and carefully examined under a light source that illuminated the exposed lumen. The anatomic orientation of the segment was maintained by assigning 4 quadrant labels relative to the myocardial surface of the artery. The luminal surface of the exposed artery was immersed in nonionic green dye for 12 h before cutting. The dye was then gently washed off the arterial surface, and the specimens were fixed and sectioned. Areas of obvious rupture and ulceration of the vessel wall (based on histologic evidence of a major communication between the plaque and the lumen) incorporated and retained the green dye within the plaque, whereas no visual evidence of the dye could be found in other areas. Hence, the presence of green dye within a plaque that had possibly ruptured based on histologic exam was considered evidence that a precutting rupture was present.

In the larger, more proximal segments, 2 longitudinal quadrants 180° apart were processed for further histologic examination; in smaller, more distal segments, only 1 quadrant was processed. The specimens were fixed in formalin, and then decalcified for approximately 24 h to avoid tissue distortion during processing. All specimens were embedded in paraffin. Fixation and embedding were performed in identically programmed Renaissance (Ventana Medical Systems Inc., Tucson, Arizona) or VIP (Tissue Tek, Sakura Finetek, Inc., Torrance, California) tissue processors. Quadrants were cut longitudinally at 4 to 5 μm, and parallel slides were stained with hematoxylin and eosin and the combined Verhoeff elastic-Gomori trichrome technique. High-resolution digital photographs of all slides were acquired (QImaging, Ratiga 1300i, Olympus BX40, Surrey, British Columbia, Canada).

Plaque analysis. During longitudinal sectioning of 20-mm coronary segments, the ends were manually pinned down to a tissue block. Although we processed the entire 20-mm segment through histology, we chose not to include 2.5-mm intervals on either end of each segment in our digital image analysis, out of concern that the tissue fixtures (pins) might cause artifactual damage. The middle 15 mm of each digital

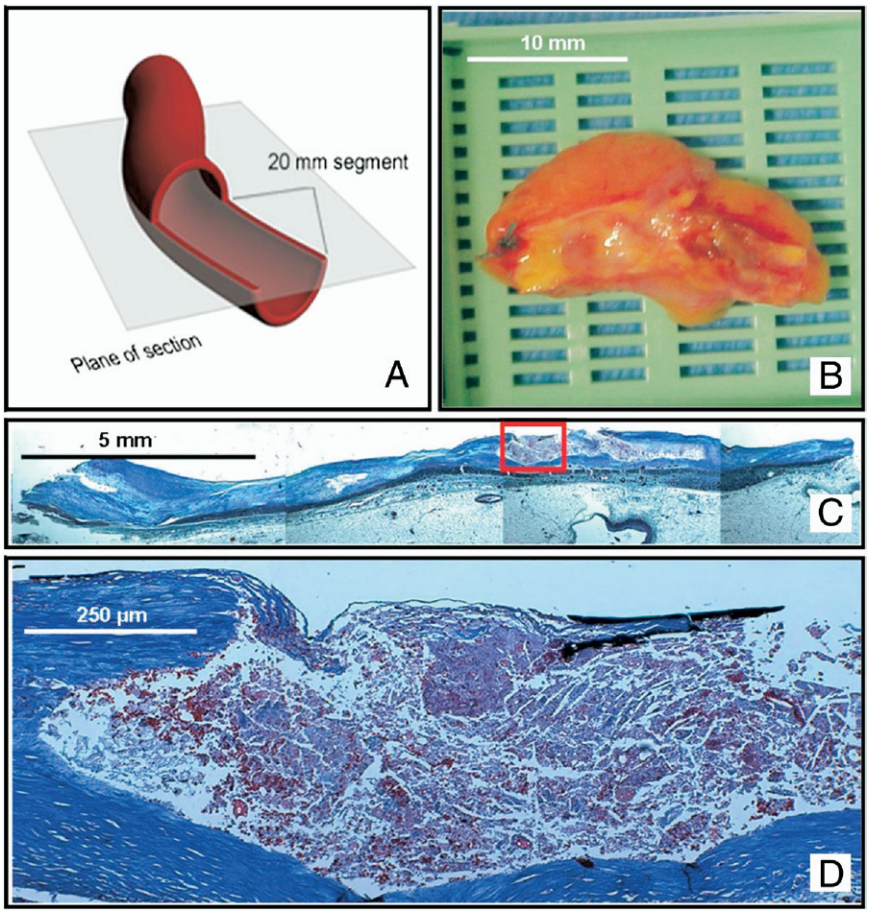


Figure 1 **Longitudinal Sectioning of Coronary Tissue**

This section was taken from a 78-year-old Caucasian man, 1 week status postmyocardial infarction, who died of a cerebrovascular accident. **(A and B)** Coronary arteries cut longitudinally at 20-mm increments to expose the vessel lumen. **(C)** Histology of a representative section visualized with the combined Verhoeff elastic-Gomori trichrome stain. **Red box expanded in D** displaying a thin-capped fibroatheroma characterized by a large lipid-rich necrotic core overlaid by a thin fibrous cap.

image of the tissue was graphically subdivided into five 3-mm intervals for the purposes of analysis. All together, 3,639 longitudinal intervals of length 3 mm were examined in 148 coronary arteries, accounting for 10.9 m of total coronary length. Order, location, and parent heart information was recorded for all 3-mm intervals. An experienced technician, who was trained in the histologic analysis of this dataset by a cardiac pathologist (R.V.), processed and classified the specimens. The intervals were classified by the technician as belonging to one of the following groups: ruptured plaque, TCFA, medium-cap fibroatheroma (MCFA), thick-cap fibroatheroma (ThCFA), or other. For each ruptured plaque, 2 criteria were required: 1) presence of a necrotic core or lipid pool of any size; and 2) the presence of green dye (described previously) in direct contact with the lipid pool or necrotic core. For each plaque, these features were confirmed by the lead investigator (P.K.C.). Definitions for the groups were derived from the Virmani-modified American Heart Association scheme described previously (35). All spots classified as fibroatheroma contained a nonzero necrotic area. Designation as TCFA required a minimum fibrous cap thickness <65 μm; MCFA, between 65 and 100 μm; and ThCFA, >100 μm. Classification as ruptured plaque required the presence of a necrotic core and that the lipid and/or necrotic core contacted the lumen of the vessel (documented by presence of dye injected into the artery before sectioning). When the core of a plaque was continuous across several 3-mm segments and represented a single lesion, the most advanced plaque classification (ruptured plaque $>$ TCFA $>$ MCFA $>$ ThCFA) was used as to label all segments spanned by the plaque.

The morphometry of each 3-mm interval was quantified with planimetry measurements utilizing image analysis software. Boundaries of vessel components corresponding to necrotic core, lipid pools, fibrous cap, and intima were drawn onto digital images of histologic sections using ImagePro software (Media Cybernetics, Silver Spring, Maryland). Plaque component areas were calculated from the human-specified boundaries using BioQuant software (Image Analysis Corporation, Nashville, Tennessee).

Table 1 Clinical Characteristics at Time of Death

Characteristics	Overall (n = 50)	CV Death (n = 33)	Non-CV Death (n = 13)
Demographic profile			
Male gender, n	32 (64)	22 (44)	7 (14)
Mean ± SD age, yrs	73.0 ± 9	71.8 ± 10	72.8 ± 8
Medical history, n			
Hypertension	12 (24)	9 (18)	3 (6)
Prior MI	8 (16)	5 (10)	3 (6)
Prior presentation of CHF	6 (12)	5 (10)	0 (0)
Chronic smoker	5 (10)	3 (6)	0 (0)
Prior CABG	4 (8)	4 (8)	0 (0)
NIDDM	4 (8)	4 (8)	0 (0)
IDDM	3 (6)	3 (6)	0 (0)
Cause of death, n			
CV-related	33 (66)		
MI		14 (28)	
Cerebrovascular accident		8 (16)	
Cardiac arrest		5 (10)	
Cardiomyopathy		1 (2)	
CHF		3 (6)	
Other cardiac		2 (4)	
Non–CV-related	13 (26)		
COPD			5 (10)
Cancer			3 (6)
Pulmonary embolism			1 (2)
Septicemia			1 (2)
Other			3 (6)
Unknown	4 (8)		

Values in parentheses are %.

CABG = coronary artery bypass graft; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; CV = cardiovascular; IDDM = insulin-dependent diabetes mellitus; MI = myocardial infarction; NIDDM = noninsulin-dependent diabetes mellitus; SD = standard deviation.

Statistical analysis. Continuous data are expressed as mean ± standard deviation. The 2-tailed Student *t* test was used to assess the significance of differences between 2 sample means in the absence of nesting. To account for the fact that variability in coronary lesion morphology may reflect interarterial and/or interindividual differences, rather than reflecting true differences among the morphologies of coronary plaque subtypes, a nested analysis of variance (ANOVA) was implemented to compare more than 2 lesion class means when nesting was present. A hierarchical tree was constructed to describe the relationships among the lesions that were found, nesting them first within epicardial coronary arteries (left anterior descending coronary artery, left circumflex artery, right coronary artery) and second within donor hearts. To determine whether coronary lesions were randomly distributed, we first divided the vessel distances into 20-mm categories. Following Wang et al. (22), if coronary lesions were equally likely to occur across the vessel distance categories, we assumed that the observed number of lesions would be approximately uniformly distributed. We used the chi-square test to test this assumption, and separately to assess the significance of differences between categorical variables. A p value of <0.05 was considered statistically significant.

Results

Baseline characteristics and lesion prevalence. Fifty whole hearts were received and analyzed within 72 h of death. The donors ranged in age from 55 to 93 years with a mean age of 73 years. Sixty-four percent (64%) of the hearts were from male donors (Table 1).

A total of 212 advanced coronary lesions (defined as ruptured plaque and fibroatheroma) were identified and classified as follows: 19 (9.0%) ruptured plaque, 23 (10.8%) TCFA, 23 (10.8%) MCFA, and 147 (69.3%) ThCFA (Table 2). The prevalence of advanced lesions was 100% (i.e., every heart in the study contained at least 1 fibroatheroma or ruptured plaque). Men contained significantly more advanced lesions of all types than women (5.13/heart vs. 2.67/heart, $p < 0.001$), and the CV group contained significantly more advanced lesions of all types than the non-CV group (4.67/heart vs. 3.08/heart, $p < 0.001$).

One or more TCFAs were present in the coronary arteries of 14 hearts (28%), 1 or more ruptured plaques were present in the coronary arteries of 14 hearts (28%), and 8 hearts (16%) contained both TCFA and ruptured plaque. Among the 20 hearts with at least 1 ruptured plaque or TCFA, the mean number of TCFA was 1.15 ± 1.23 per heart, and the mean number of ruptured plaques was 0.95 ±

Table 2 Distribution of Ruptured Plaque and Fibrous Cap Atheroma by Gender, Cause of Death, and Presence of Rupture

	n	Ruptured Plaque	Fibrous Cap Atheroma			Total	p Value (Chi-Square)
			Cap <65 μm	65 μm ≤ Cap <100 μm	Cap ≥100 μm		
Men	32	14 (0.44)	20 (0.63)	15 (0.47)	115 (3.59)	164 (5.13)	<0.001
Women	18	5 (0.28)	3 (0.17)	8 (0.44)	32 (1.78)	48 (2.67)	
CV	33	15 (0.45)	18 (0.55)	18 (0.55)	103 (3.12)	154 (4.67)	<0.001
Non-CV	13	4 (0.31)	4 (0.31)	3 (0.23)	29 (2.23)	40 (3.08)	
(+) rupture	14	19 (1.36)	17 (1.21)	4 (0.29)	55 (3.93)	95 (6.79)	<0.001
(−) rupture	36	0 (0)	6 (0.17)	19 (0.53)	92 (2.56)	117 (3.25)	
Total	50	19 (0.38)	23 (0.46)	23 (0.46)	147 (2.94)	212 (4.24)	

Entries indicate number of plaques, and values in parentheses represent average number of plaques per patient in each group.

CV = cardiovascular.

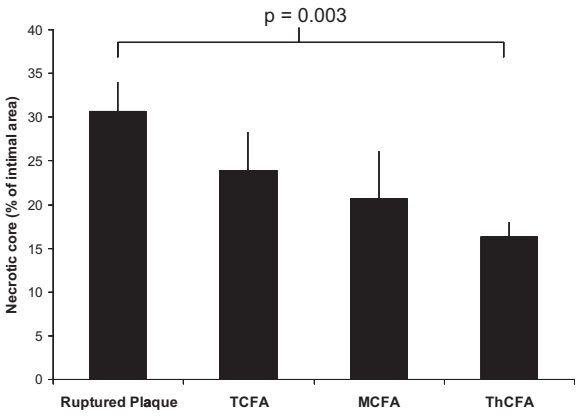


Figure 2 Necrotic Core Size of Advanced Coronary Lesions

The mean necrotic core size of thick-capped fibroatheroma (ThCFA) was significantly lower than the necrotic core size of ruptured plaques in our study. Mean necrotic core size is reflected as a percentage of intimal area for ruptured plaque and fibrous cap atheroma. MCFA = medium-capped fibroatheroma; TCFA = thin-capped fibroatheroma.

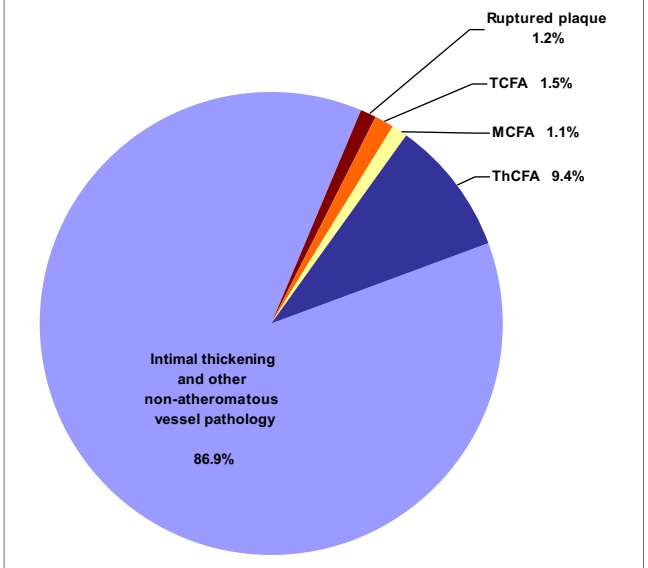


Figure 3 Frequency of Advanced Coronary Lesions

Frequencies of ruptured plaque and fibrous cap atheroma in all hearts studied are provided as a percentage of the total 3,639 coronary intervals of length 3 mm examined. Nonfibroatheromatous intervals accounted for the majority of coronary intervals, where TCFA and ruptured plaque together were observed in 2.7% of the coronary intervals. Abbreviations as in Figure 2.

0.83 per heart. Among the 14 hearts with at least 1 ruptured plaque, the incidence of TCFA (1.21 ± 1.48/heart) was significantly higher compared with hearts with no ruptured plaque (0.17 ± 0.38/heart, $p < 0.001$).

Plaque morphometry. Necrotic core area measured in absolute terms was significantly greater in ruptured plaque (2.2 ± 1.9 mm^2) than ThCFA (1.1 ± 1.4 mm^2, $p < 0.001$), and significantly greater in TCFA (1.6 ± 1.8 mm^2) than ThCFA ($p = 0.028$). As a percentage of intimal area, necrotic core size was significantly different between ruptured plaque and ThCFA (31.0 ± 3.6% vs. 17.2 ± 1.8%, $p = 0.0034$), though similar for all other pairs (Fig. 2).

Thick-capped fibroatheroma also had significantly longer fibrous caps in longitudinal section (6.3 ± 3.5 mm) than other advanced coronary lesions (Table 3) (not shown: $p < 0.05$ for each *t* test pair). No difference could be found in necrotic core length (2.7 ± 2.0 mm and 1.9 ± 3.6 mm, respectively) or fibrous cap length (5.4 ± 2.8 mm and 4.2 ± 2.7 mm, respectively) between TCFA and ruptured plaque. Under a nested ANOVA analysis, interartery or interindividual differences in the measured morphologic variables of a single class of advanced coronary lesion were not significant ($p > 0.05$).

Frequency of TCFA and ruptured plaque. To compensate for variations in plaque length, we analyzed the number of short (3-mm) coronary segments as well as unique coronary plaques. Of 3,639 short coronary segments analyzed, only 53 (1.5%) were classified as TCFA and 44 (1.2%) as ruptured plaque (Fig. 3).

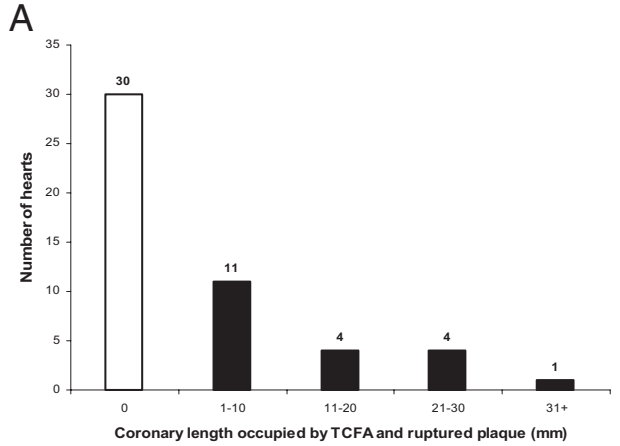
In patients dying of CV causes, 41 of 2,574 segments (1.6%) were classified as TCFA, and 31 of 2,574 (1.2%) were classified as ruptured plaque. In patients dying of non-CV or unknown causes, 12 of 1,065 segments (1.1%) were classified as TCFA, and 13 of 1,065 segments (1.2%) were classified as ruptured plaque.

In total, 30 hearts (60%) contained no ruptured plaque or TCFA. In 11 of the 20 hearts containing 1 or more TCFA

Table 3 Morphometric Dimensions of Ruptured Plaques and Fibrous Cap Atheromata

		Fibrous Cap Atheroma			
	Ruptured Plaque (n = 19)	Cap <65 μm (n = 23)	65 μm ≤ Cap <100 μm (n = 23)	Cap ≥100 μm (n = 147)	ANOVA
Minimum cap thickness, μm	0*	44 ± 18	79 ± 19	232 ± 135	<0.001
Length of fibrous cap, mm	4.2 ± 2.7	5.4 ± 2.8	3.7 ± 1.7	6.3 ± 3.5	0.17
Necrotic core area, mm^2	2.2 ± 1.9	1.6 ± 1.8	1.3 ± 3.6	1.1 ± 1.4	0.63
Length of necrotic core, mm	1.9 ± 3.6	2.7 ± 2.0	N/A	N/A	0.29

Values are reported as mean ± standard deviation. *By definition ruptured plaques have an observable minimum cap thickness of zero.
ANOVA = analysis of variance; N/A = data not available.



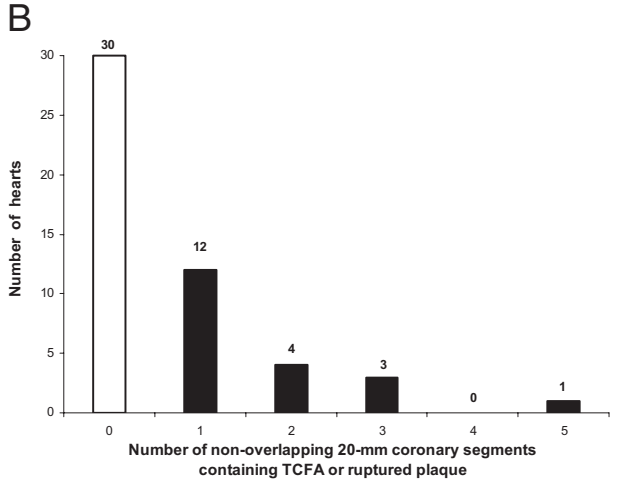


Figure 4 **Focal Distribution of TCFA and Ruptured Plaque**

Twenty of 50 hearts in our study (20 of 50) contained at least 1 thin-capped fibroatheroma (TCFA) or ruptured plaque. **(A)** A majority of these hearts (11 of 20) contained TCFA and ruptured plaque within 10 mm or less of coronary tissue. **(B)** In addition, a majority of the 20 hearts (12 of 20) contained TCFA and ruptured plaque within a single, contiguous 20-mm coronary segment. In 1 heart with widely distributed fibroatheromatous disease, 5 such 20-mm segments were required to contain all instances of TCFA and ruptured plaque.

or ruptured plaques (55%), these lesions accounted for <10 mm of total coronary length (Fig. 4A). Moreover, ruptured plaque and TCFA were often clustered, being contained within 2 or fewer nonoverlapping 20-mm coronary segments in 16 of the 20 hearts (80%) containing these lesions (Fig. 4B).

Spatial distribution of TCFA and ruptured plaque. Ruptured plaques and TCFA clustered in the proximal left anterior descending and left circumflex arteries (Figs. 5A and 5B); 50% of all ruptured plaques and TCFA were present within the first 22 mm, and 90% within the first 33 mm of the left anterior descending and left circumflex arteries (Fig. 6). Within the right coronary artery, 50% of all ruptured plaques and TCFA were observed within the first 31 mm, and 90% within the first 74 mm (Fig. 6).

Discussion

Our findings demonstrate that TCFA and ruptured plaques in human coronary arteries are infrequent and focally distributed. On average, TCFA and ruptured plaque occupied <3% of the coronary artery length examined. These structures clustered in the proximal left anterior descending coronary artery and left circumflex artery, and were more uniformly distributed in the right coronary artery. These findings, which were obtained with a novel longitudinal sectioning method and aided by computerized morphometry, reinforce and extend previous findings obtained by serial transverse sectioning (8,36,37). Prior autopsy studies reporting a low frequency of these structures had been criticized for the possibility that TCFAs and ruptured plaques could have been missed if they occurred in the tissue between cross sections. The present study, with its longitudinal sectioning, is not subject to this criticism and yielded a similar answer. Since TCFA and ruptured plaques are considered to be precursors of intracoronary thrombi, these findings support the testing of vulnerable plaque detection and treatment strategies.

Frequency of TCFA and ruptured plaque. Thin-capped fibroatheroma and ruptured plaque are prevalent disease entities—20 of 50 hearts examined (40%) in our study contained at least 1 such lesion. Yet, within a given heart, the lesions are not frequent; on average, each of the 20 hearts contained only 2.1 ± 1.7 TCFA and/or ruptured plaques. Moreover, when present, these lesions clustered within only 1 or 2 nonoverlapping 20-mm segments in 80% of cases. The finding in the present study that approximately 20% of hearts had more than 1 TCFA or ruptured plaque is compatible with clinical findings (38,39) that about 10% of patients undergoing a stenting procedure experience a clinical event in the following year that is caused by a second lesion. Thus, the suspected precursor lesions to ACS and sudden death are prevalent within the population, but infrequent and focally distributed in individuals.

As expected, the frequency of TCFA and ruptured plaques was greater in individuals dying of a CV cause than in those dying of non-CV or unknown causes. Thin-capped fibroatheroma were also more likely to be found in patients with a ruptured plaque elsewhere in the coronary arterial tree. The incidence of TCFA in hearts that contained at least 1 plaque rupture was 1.21/heart, which is similar to the incidence of 1.22 TCFA/heart reported by Farb et al. (8) in victims of sudden coronary death.

Previous reports of TCFA frequency using clinical imaging tools such as intravascular ultrasound imaging and angioscopy (7,40) have suggested much higher frequencies, with as many as 3.0 TCFA/cm reported in ACS patients. The limitations of these imaging tools, however, prevent an accurate determination of cap thickness and plaque composition and do not enable one to reliably differentiate lipid and fibrotic tissue (41). Intravascular ultrasound, a promising in-vivo technology, currently has a resolution in the

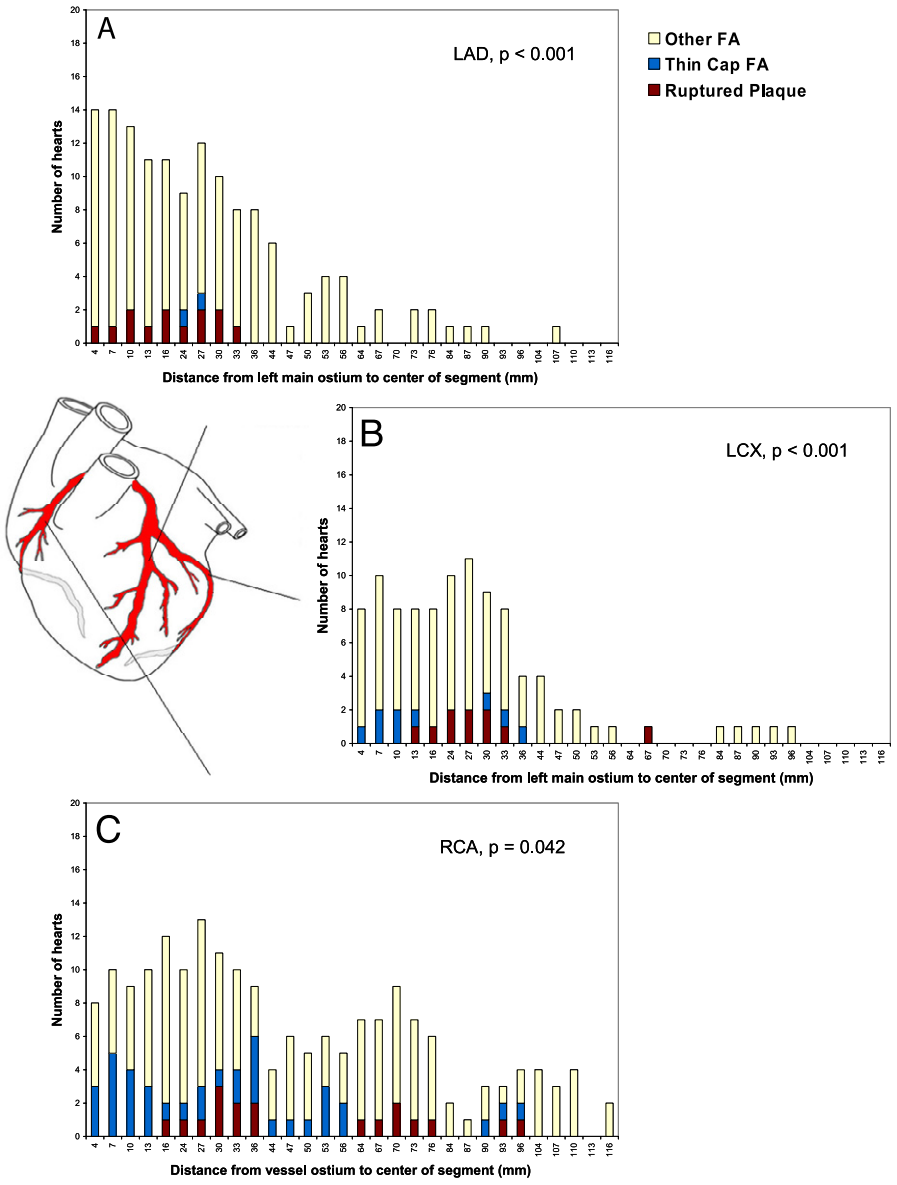


Figure 5 **Spatial Distribution of Advanced Coronary Lesions**

The number of hearts with ruptured plaque, thin-capped fibroatheroma (FA), and other FA, in millimeters from the coronary vessel ostium. **(A)** Left anterior descending artery (LAD). **(B)** Left circumflex artery (LCX). **(C)** Right coronary artery (RCA).

range of 100 to 200 μm (42), which is too coarse to distinguish TCFA from medium and ThCFA. Similarly, color intensity mapping by angioscopy is known to classify plaques as vulnerable, which do not correlate with TCFA or ruptured plaque by histology (43). Histologic examination, which is the gold-standard for detection of TCFAs and ruptured plaques, enables one to assess the native error in these in-vivo imaging techniques.

Despite the low frequency of TCFA and ruptured plaques in the present report, there was evidence of a pan-coronary process of atherosclerotic involvement in select patients; when 1 ruptured plaque was present, 1 or more additional ruptured plaques were present in 28.6% of cases. This finding of multiple advanced plaques is consistent with a prior angiographic study, which identified multiple complex plaques in 40% of patients with acute myocardial infarction (20).

Spatial distribution of TCFA and ruptured plaque. Our longitudinal sectioning data confirm prior cross-sectional analyses by Farb et al. (8) and Davies (44) indicating that TCFA and ruptured plaques are concentrated in the proximal portions of the left anterior descending and left circumflex coronary arteries and are more uniformly distributed in the right coronary artery. This accumulated autopsy

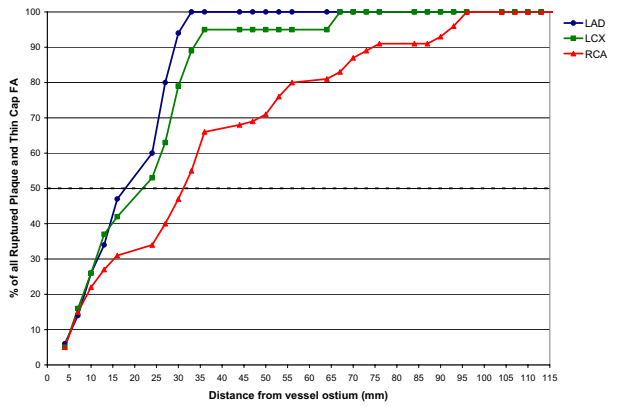


Figure 6 **Cumulative Frequency Distribution of TCFA and Ruptured Plaque**

The cumulative frequency distribution curve of thin-capped fibroatheroma (TCFA) and ruptured plaque in each of 3 coronary arteries demonstrates a more diffuse distribution of these lesions in the RCA than in either branch of the left main coronary artery. Abbreviations as in Figure 5.

evidence fits well with angiographic studies that have demonstrated similar locations of the culprit lesions causing ACS (22). The localization of TCFA in the same regions where ruptured plaques and angiographic culprit lesions have been found supports the concept that TCFAs are the precursor lesions to rupture and thrombosis. This geographic concentration of risk also supports the feasibility of efforts to invasively identify vulnerable plaque with catheter-based systems discriminating plaque morphology, chemical composition, or metabolic activity.

Several explanations have been put forward to explain the tendency of advanced plaques to develop preferentially in certain anatomic locations. The tortuosity and frequent branching of certain portions of the coronary vessels result in significant variations in shear stress (45). Low shear stress has been implicated in the migration of lipids and monocytes into the vessel wall (45), processes that could accelerate the progression of an atherosclerotic lesion towards a TCFA and ruptured plaque.

Relationship between necrotic core size, cap thickness, and plaque rupture. Our finding of an inverse relationship between necrotic core size and cap thickness in a variety of advanced lesions is similar to that reported in a study of sudden coronary death victims (37). The mean necrotic core size was greatest in ruptured plaques, followed by TCFA, and then other fibroatheromas, suggesting that as the necrotic cores of TCFA enlarge they may become more likely to rupture. The association of increased necrotic core size with plaque rupture is still compatible with observations that ruptures frequently occur at sites of low percentage stenosis because outward remodeling may occur.

The pathophysiology underlying the inverse relationship between necrotic core size and reduction in cap thickness is unknown. Activated macrophages in necrotic core secrete matrix metalloproteases and collagenases (46), which may retard the development of a thick, protective, collagen-rich cap through direct degradation of matrix proteins and by antagonizing the actions of smooth muscle cells. Alternatively, the presence of a thick fibrous cap may act as a physical barrier to the migration of inflammatory cells from the lumen, resulting in diminished growth of the necrotic core. A consequence of the inverse relation between cap thickness and necrotic core size is that plaques that are most susceptible to rupture also contain the greatest amount of thrombogenic necrotic material.

Study limitations. Several limitations of the present analysis should be appreciated. First, the hearts were obtained from a research tissue procurer (National Disease Research Interchange), and are not a representative sample of the general population or a specific subset of patients. Second, because of confidentiality issues, certain historical information was unavailable, for example, serum cholesterol levels before death. Third, preparation of the samples included flushing, which would wash out luminal thrombi, precluding detection of culprit lesions and estimation of the frequency of erosion sites, the second most frequent cause of acute coronary thrombosis (47). Fourth, the longitudinal sectioning did not sample all portions of the artery; approximately 25% of coronary length was not sampled due to handling of tissue specimens, and in segments that were sampled, eccentric plaques occupying $<180^{\circ}$ of arc could have been missed since, at most, 2 sections were made on opposite sides of the artery. However, the majority of TCFA occupy $>180^{\circ}$ of arc (48), and thus it is unlikely that the principal conclusions regarding precursor lesion frequency and focality would be altered. Fifth, since this study is autopsy-based, we have no information on the temporal course of vulnerability. Thin-capped fibroatheroma and ruptured plaques may arise and resolve quickly (49), or they may develop gradually over many years—in either case, the time course of these lesions cannot be definitively identified from histologic 'snapshots' provided by autopsy specimens.

Implications of focality of suspected precursor lesions for detection and treatment of vulnerable plaque. The findings of the present study are of considerable importance for the ongoing debate regarding the focal versus systemic features of the mechanism through which atherosclerosis produces clinical events. The vital question concerns the distribution of risk along the length of a coronary artery—is risk concentrated in a single or small number of sites that could be identified and treated before an event, or is risk driven by a systemic process and distributed in a relatively uniform manner throughout the artery? The limited, focal occurrence of TCFA and ruptured plaques observed in our study, and the predilection of these presumably high-risk structures to occur in certain portions of the coronary vessels, supports the proposition that coronary risk is concentrated in a relatively circumscribed segment of the coronary arterial tree. It is well known that the high-risk

lesions that cause events in many cases do not cause flow limitation before their rupture (4,14,37). Our finding of a focal distribution of suspected precursor lesions supports efforts to develop novel tools to identify these structures that may occur at sites with and without flow-limiting stenoses. If such locations could be identified, and treated by focal, regional, or systemic therapy, it may be possible to reduce the high incidence of secondary coronary events that currently occur in ACS patients despite application of the best therapeutic options available (34,50,51).

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Reprint requests and correspondence: Mr. Pavan K. Cheruvu, 104 Toxteth Street, #4, Brookline, Massachusetts 02446. E-mail: pavan_cheruvu@hms.harvard.edu.

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